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TECHNICAL REPORT

Infection Casualty Estimation (ICE) Model: Predicting Sepsis in Nuclear Detonation Burn Patient Populations using Procalcitonin as a Biomarker

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14. ABSTRACT

Individuals exposed to nuclear weapon environments may be injured or killed from the primary blast wave, thermal pulse and ionizing radiation. Burn casualties surviving the initial blast wave are at an increased risk of developing infections that, ultimately, may result in sepsis. Sepsis, a life-threatening condition resulting from an uncontrolled systemic inflammatory response, is associated with high rates of mortality. Consequently, the risk of sepsis in burn casualties creates a significant burden on emergency departments and intensive care units (ICUs) to identify high-risk patients for early intervention and treatment. The Infection Casualty Estimation (ICE) model predicts the risk of developing sepsis as a function of the percentage of total body surface area (% TBSA) burned. This model was developed using clinical data of burn patients and measurements of procalcitonin (PCT), a biomarker of sepsis. The model predicts PCT levels of burn patients as a function of % TBSA, and compares these values to clinically derived benchmarks to predict the risk of sepsis. The ICE model can be used by medical planners to estimate expected medical burden in an IND scenario.

15. SUBJECT TERMS

Infection, Sepsis, Burn, Thermal Injury, Nuclear Weapon, Procalcitonin, Biomarker

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UNIT CONVERSION TABLE
U.S. customary units to and from international units of measurement[*]

U.S. Customary Units	Multiply by → / ← Divide by[†]		International Units
Length/Area/Volume			
inch (in)	2.54	$\times 10^{-2}$	meter (m)
foot (ft)	3.048	$\times 10^{-1}$	meter (m)
yard (yd)	9.144	$\times 10^{-1}$	meter (m)
mile (mi, international)	1.609 344	$\times 10^{3}$	meter (m)
mile (nmi, nautical, U.S.)	1.852	$\times 10^{3}$	meter (m)
barn (b)	1	$\times 10^{-28}$	square meter (m^2)
gallon (gal, U.S. liquid)	3.785 412	$\times 10^{-3}$	cubic meter (m^3)
cubic foot (ft^3)	2.831 685	$\times 10^{-2}$	cubic meter (m^3)
Mass/Density			
pound (lb)	4.535 924	$\times 10^{-1}$	kilogram (kg)
atomic mass unit (AMU)	1.660 539	$\times 10^{-27}$	kilogram (kg)
pound-mass per cubic foot (lb ft^{-3})	1.601 846	$\times 10^{1}$	kilogram per cubic meter (kg m^{-3})
Pound-force (lbf avoirdupois)	4.448 222		Newton (N)
Energy/Work/Power			
electron volt (eV)	1.602 177	$\times 10^{-19}$	joule (J)
erg	1	$\times 10^{-7}$	joule (J)
kiloton (kT) (TNT equivalent)	4.184	$\times 10^{12}$	joule (J)
British thermal unit (Btu) (thermochemical)	1.054 350	$\times 10^{3}$	joule (J)
foot-pound-force (ft lbf)	1.355 818		joule (J)
calorie (cal) (thermochemical)	4.184		joule (J)
Pressure			
atmosphere (atm)	1.013 250	$\times 10^{5}$	pascal (Pa)
pound force per square inch (psi)	6.984 757	$\times 10^{3}$	pascal (Pa)
Temperature			
degree Fahrenheit (ºF)	[T(ºF) − 32]/1.8		degree Celsius (ºC)
degree Fahrenheit (ºF)	[T(ºF) + 459.67]/1.8		kelvin (K)
Radiation			
activity of radionuclides [curie (Ci)]	3.7	$\times 10^{10}$	per second (s^{-1}[‡])
air exposure [roentgen (R)]	2.579 760	$\times 10^{-4}$	coulomb per kilogram (C kg^{-1})
absorbed dose (rad)	1	$\times 10^{-2}$	joule per kilogram (J kg^{-1}[§])
equivalent and effective dose (rem)	1	$\times 10^{-2}$	joule per kilogram (J kg^{-1}[**])

[*]Specific details regarding the implementation of SI units may be viewed at http://www.bipm.org/en/si/.

[†]Multiply the U.S. customary unit by the factor to get the international unit. Divide the international unit by the factor to get the U.S. customary unit.

[‡]The special name for the SI unit of the activity of a radionuclide is the becquerel (Bq). (1 Bq = 1 s^{-1}).

[§]The special name for the SI unit of absorbed dose is the gray (Gy). (1 Gy = 1 J kg^{-1}).

[**]The special name for the SI unit of equivalent and effective dose is the sievert (Sv). (1 Sv = 1 J kg^{-1}).

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Executive Summary

Nuclear weapon casualties with moderate to severe burns are at risk of secondary infection in health care settings. These infections cause considerable morbidity in burn patients, and infection can lead to sepsis followed by death. To the best of our knowledge, there are currently no mathematical models that predict sepsis from burn wound severity. As a result, there is a need to develop a methodology that can be used to estimate sepsis due to secondary infection in burn patients exposed to nuclear weapon environments. We have developed a model that predicts burn patient susceptibility to sepsis, utilizing clinical data and the predictive biomarker, procalcitonin.

Section 1. Introduction

The Defense Threat Reduction Agency (DTRA) has tasked the Human Survivability R&D Integrated Program Team (HSRDIPT) to develop casualty estimation models for improvised nuclear device (IND) scenarios. The HSRDIPT team has developed health effects models of radiation, burn, and blast to estimate injury severity and probability of mortality. These models include the probability of 48-hour, 30-day and 60-day mortality from combined injury exposure, as well as time-dependent response and recovery models of hematopoietic and small intestine epithelial cellular kinetics (Oldson et al. 2015; Stricklin et al. 2015). However, HENRE does not currently host a model that predicts the development/spread of infection, or the health complications resulting from infection. These health complications will have a significant impact on medical demand in the event of a nuclear weapon detonation.

This report describes a model that predicts sepsis due to burn injury as a first step in deriving a complete model of infection as a result of combined injury. We have chosen sepsis as an output for the model because it is a specific endpoint of infection that is life-threating, yet treatable, defined by specific clinical markers. Our initial focus on burn injuries is driven by the following considerations:

- For an IND detonation, burns are likely to be a significant solo injury. Data from Hiroshima and Nagasaki show significant numbers of injuries at 20 days due to thermal effects alone (Oughterson 1956).
- Thermal environments are expected to extend further than prompt radiation and blast in many scenarios. In Messerschmidt (1976), it was estimated that thermal effects will extend much further than prompt radiation and blast effects for large INDs (air burst). Flynn and Goans (2012) estimated that, for a ground burst IND (unshielded), the radius for receiving second degree burns over 50% TBSA is much larger than the LD_{50} radius for other injury types.
- Contemporary burn management is resource-intensive and likely to dominate the burden of medical staff and supplies post-IND detonation. Estimating medical demand of IND scenarios is critical for the future development of HENRE, which will eventually be integrated with medical and emergency management planning tools.
- Burn injuries provide a well-defined clinical estimation of the insult (% TBSA), and a large body of data exists on burn injury outcomes and biomarkers to aid in model construction.

The ultimate goal of this effort is to provide HENRE with a deterministic model of infection based on available data, including data on biomarkers and the full range of clinical outcomes. For the current model, we have used procalcitonin (PCT) as a biomarker to model the probability of sepsis for burn casualties. We have decided to incorporate PCT in our model for three particular reasons:

1. Serum PCT levels have been identified as a clinical indicator of sepsis, and a potentially useful tool for indicating antimicrobial treatment (Gilbert 2010; Schuetz et al. 2011; Lavrentieva et al. 2015).

2. A significant amount of data has reported the relationship between burn size (% TBSA) and PCT levels, as well as the relationship between PCT levels and the probability of sepsis.
3. A future aim of this project is to develop a mechanistic model of molecular indicators of sepsis, such as PCT. A dynamic model of biomarkers of sepsis can provide estimates of timing of infection and/or treatment requirements. Establishing the relationship between burn size, PCT and sepsis in the first phase of this model will aid in future model developments.

Section 2. Purpose

This report introduces the Infection Casualty Estimation (ICE) model, a predictive model of burn-induced sepsis providing improved casualty estimation capabilities for an IND scenario. ICE provides a simple, data-driven model for calculating the probability of sepsis as a function of burn % TBSA.

In the aftermath of an IND detonation, it is important to develop accurate predictions of casualty streams to assist medical and emergency management planning. A large number of casualties will be in need of medical treatment for radiation, burn and blast injuries, placing a significant burden on health care professionals and raising the demand for medical supplies in the blast region. Estimating the response and recovery to these insults is valuable for providing realistic estimations of decontamination, triage, and long-term recovery. ICE is a preliminary model for predicting septic casualties from nuclear weapon environments. The first phase of this model focuses on burn injuries, and includes one of the most reliable biomarkers of burn-induced sepsis to date. The ICE model uses burn severity to estimate PCT levels, and subsequently predicts the probability of sepsis from PCT levels (Figure 1). This model will provide HENRE with additional casualty estimation details that can be useful for predicting the medical burden imposed by a nuclear weapon scenario.
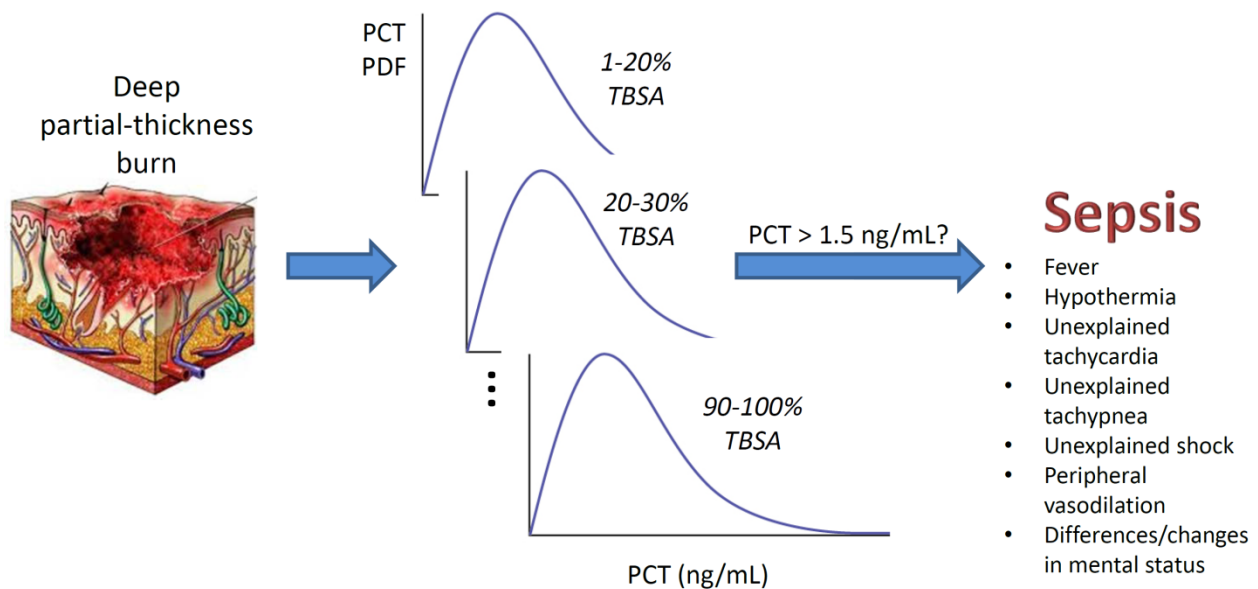

Figure 1. ICE model diagram.

Section 3. Background

The following section provides background relevant to the development of the ICE model. Section 3.1 describes the use of % TBSA, the input to the ICE model, as an estimate of burn severity. In Sections 3.2 and 3.3, infection, sepsis, and their relationships to burn injury are discussed. Finally, we discuss the relationship between procalcitonin levels and % TBSA, as well as the evidence that procalcitonin is a reliable biomarker for sepsis (Section 3.4).

3.1 Assessing the Extent of Burn Wounds

Burn injuries are often measured with visual estimation methods, three of which are most commonly used in practice. The most widely used method is the Wallace Rule of Nines. The Rule of Nines divides the body into 9% surface area sections, approximates the amount of burn on each of these sections, and adds these estimates to approximate the percentage of the total body surface area (% TBSA) burned (Hettiaratchy and Papini 2004; Church et al. 2006; Roth and Hughes 2015). The Rule of Nines is considered inaccurate for children due to their proportionally larger head sizes; therefore, an alternate Rule of Nines for Children was published with more accurate burn size dimension to account for observed discrepancies (Schiller 1996). The most accurate method is the Lund and Browder chart, which also provides an estimate of % TBSA burned on an individual (Hettiaratchy and Papini 2004; Church et al. 2006; Roth and Hughes 2015). This method is more accurate than the Rule of Nines because it divides the body into smaller regions, and provides different head proportions for six age groups. Lastly, the Palmer surface method estimates relatively small burns by using the size of one's palm (roughly 0.8% of the full body) as a measuring tool; however, this method does not accurately represent medium to large burns (Hettiaratchy and Papini 2004).

The above methods provide systematic approaches for establishing % TBSA estimates of burn patients. The % TBSA measurement is a quickly attainable and reliable assessment of burn severity, which is indicative of a patient's susceptibility to infection (D.W. Buck 1995; Kagan et al. 2013).

3.2 Infection

Infection is a serious risk for moderate to severe burn casualties due to the amount of epidermis, dermis, and subcutaneous tissue exposed (Abdullahi et al. 2014). Infections are one of the most serious complications to result from a burn trauma (Church et al. 2006; Gomez et al. 2009; Keen et al. 2010), and burn-induced infection can lead to sepsis, one of the most common causes of death after severe burns (Milenkovic et al. 2007). While burn treatment in hospitals has evolved over the past 50 years to include intense grafting and applicable stem-cell research, the recommendation for pre-hospital and standard care has remained largely unchanged (Roth and Hughes 2015; Rowan et al. 2015).

The potential for environmental and nosocomial (hospital-acquired) infection of a burn wound has remained unchanged in many exposure environments for civilian populations. However,

military burn casualties operating in austere environments may have a longer delay before receiving advanced care (Wolf et al. 2006; Keen et al. 2010). Delay in extensive treatments such as excision and skin grafting can increase the incidence of sepsis (Lloyd and Hight 1978; D'Avignon et al. 2008).

Various bacteria, viruses, and fungi are responsible for causing infection in open wounds. Table 1, adapted from Church et al. (2006), lists the most common of these microbes reported as the cause of infection. Immediately after the initial burn, the exposed wound is sterile. Microorganisms are quick to invade and colonize the protein-rich wound surface while the patient's immunological responses are compromised (Church et al. 2006; Japoni et al. 2009). The most common infections in burns are caused by gram-positive microorganisms, which are gradually replaced by gram-negative microorganisms through interspecies competition (Wurtz et al. 1995). The gram-positive bacterium, *Staphylococcus aureus* is known to be one of the more aggressive initial colonizers in burn wounds (Church et al. 2006). Of the gram-negative bacteria, *Pseudomonas aeruginosa* closely followed by *Escherichia coli* are major colonizers of burn wounds (Church et al. 2006). In many prospective studies, *Pseudomonas aeruginosa* has displayed the ability to outcompete other microorganisms as an opportunistic pathogen, and it is hypothesized that this may be attributed to its presence as a nosocomial infection (Japoni et al. 2009).

Nosocomial infections in burn patients have become an increasing concern for health care professionals (Branski et al. 2009; Posluszny Jr et al. 2011), particularly with the increase usage of antibiotics (Khan et al. 2015). Common bacteria responsible for nosocomial infections include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Methicillin-resistant Staphylococcus aureus*, and *Escherichia coli* (the same bacteria infecting burn patients as seen in Table 1). Ongoing research of infection prevention is being conducted and implemented (Khan et al. 2015).

Table 1. Common pathogens causing infection in burn patients (Church et al. 2006).

Type*	Microbes*	Hospital (nosocomial)**
Gram-positive organisms	Staphylococcus aureus	Yes
	Methicillin-resistant S. aureus	Yes
	Coagulase-negative staphylococci	Yes
	Enterococcus spp.	Yes
	Vancomycin-resistant enterococci	Yes
Gram-negative organisms	Pseudomonas aeruginosa	Yes
	Escherichia coli	Yes
	Klebsiella pneumoniae	Yes
	Serratia marcescens	Yes
	Enterobacter spp.	Yes
	Proteus spp.	Yes
	Acinetobacter spp.	Yes
	Bacteroides spp.	No
Fungi	Candida spp.	Yes
	Aspergillus spp.	Yes
	Fusarium spp.	Yes
	Alternaria spp.	Yes (emerging, not common)
	Rhizopus spp.	Yes (not common)
	Mucor spp.	Yes
Viruses	Herpes simplex virus	Yes (very rare)
	Cytomegalovirus	No
	Varicella-zoster virus	Yes

* List of pathogens from Church et al. (2006)
** Nosocomial information from various sources (Bottone et al. 1979; Hanley et al. 1993; Fridkin and Jarvis 1996; Aitken and Jeffries 2001; Groll and Walsh 2001; von Eiff et al. 2001; Church et al. 2006; Perlroth et al. 2007; Wick and Sears 2010; Gomes et al. 2011; Keim et al. 2011; Olawale et al. 2011; E.C. Lloyd 2012; Khan et al. 2015)

3.3   Sepsis from Burn

Infection is defined as an establishment of a pathogen in its host after invasion causing disease (Groll and Walsh 2001). Sepsis is the physiological reaction to the infectious agent in an overactive, inflammatory response. The precursor to sepsis, systemic inflammatory response syndrome (SIRS), is the systematic activation of the innate immune response (Levy et al. 2003). SIRS can be triggered by many injuries, and is not exclusive to infection (Kaplan 2017). Therefore, sepsis can be considered SIRS with the addition of infection (Levy et al. 2003). Sepsis can progress to severe sepsis and septic shock if left untreated. Severe sepsis is defined as sepsis accompanied by organ dysfunction (also hypotension or hypoperfusion) (Matot and Sprung 2001; Levy et al. 2003). Septic shock is characterized by all aspects of severe sepsis with the added complication that the patient is unresponsive to adequate fluid resuscitation, which often leads to death (Matot and Sprung 2001). The interrelationships between infection, sepsis and SIRS are shown in Figure 2.
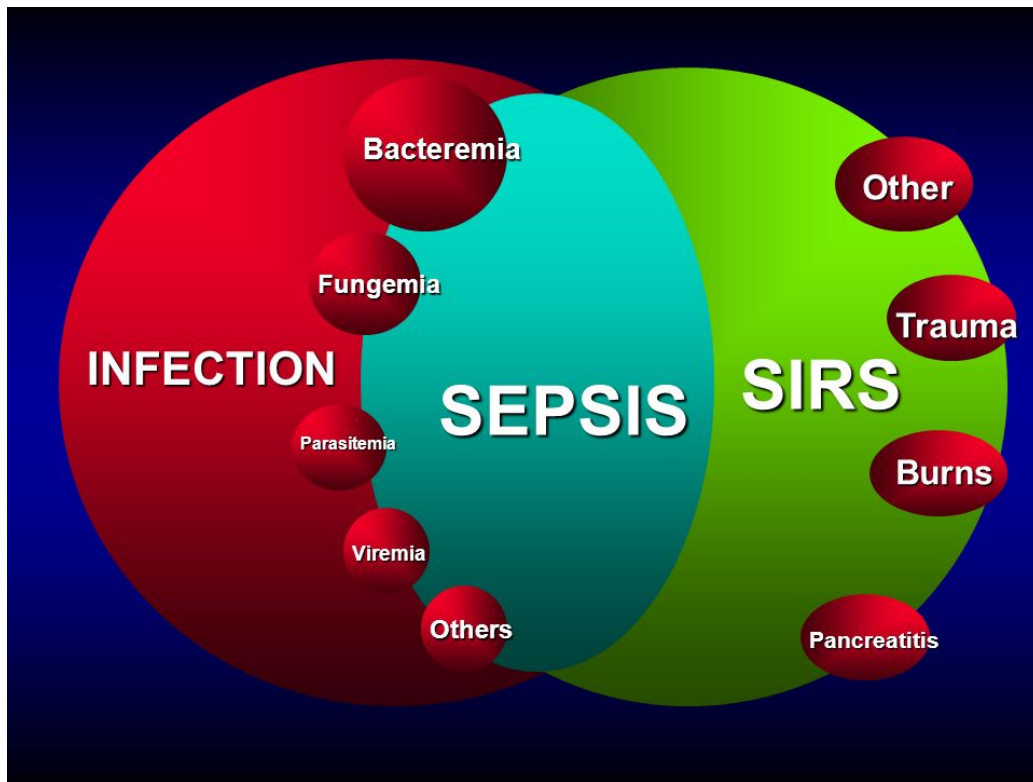
Figure 2. Causes of and relationships between infection, sepsis and SIRS (Kell and Pretorius 2015).

Sepsis is a major cause of death for individuals who have sustained severe burn injuries (Chipp et al. 2010; Rowan et al. 2015). Recent data from two separate burn centers identified infection as the cause of mortality for 21.3% of observed patients (Bloemsma et al. 2008). Although unproven, sepsis was highly suspected as the cause of mortality in another 24.6% of the observed individuals.

The definitions of sepsis, SIRS, and septic shock were standardized in a 1991 consensus conference. In 2007, the definitions for sepsis among burn patients were amended and the category of "Severe Sepsis" was dropped on the grounds that it is very rare for a burn patient to have an intermediate phase between the sepsis stage and the septic shock stage (Greenhalgh et al. 2007). The definitions were revisited again in 2016, and the definition of sepsis was updated to "life-threatening organ dysfunction caused by a dysregulated host response to infection" (Singer et al. 2016).

It has been established that three or more of the triggers provided in Table 2 indicates sepsis (Greenhalgh et al. 2007). This allows for a precise diagnosis through metabolic, physiologic, and immunologic changes, especially in the case of burn patients.

Table 2. Triggers of sepsis as defined in Greenhalgh et al. (2007).

Trigger	Diagnostic Symptoms
Temperature	>39° or < 36.5°C
Progressive Tachycardia	Adults >110 bpm. Children >2 SD above age-specific norms (85% age-adjusted max heart rate).
Progressive Tachypnea	Adults > 25 bpm not ventilated. Minute ventilation 121/min ventilated. Children > 2 SD above age-specific norms (85% age-adjusted max respiratory rate).
Thrombocytopenia	Adults < 100,000/mcl. Children <2 SD below age-specific norms. (will not apply until 3 days after initial resuscitation).
Hyperglycemia	Untreated plasma glucose >200 mg/dl or equivalent mM/L. Insulin resistance—examples include >7 units of insulin/hr intravenous drip (adults), significant resistance to insulin (>25% increase in insulin requirements over 24 hours). (in the absence of pre-existing diabetes mellitus).
Inability to continue enteral feedings 24 hours	Abdominal distension. Enteral feeding intolerance (residual >150 ml/hr in children or two times feeding rate in adults). Uncontrollable diarrhea (>2500 ml/d for adults or >400 ml/d in children).
Documented Infection	Culture positive infection, or Pathologic tissue source identified, or Clinical response to antimicrobials

In burn patients, sepsis is best treated and eliminated if identified early (von Heimburg et al. 1998). Clinical signs and measured laboratory parameters can help predict the often sudden onset of sepsis in burn patients. The clinical signs of sepsis include (Matot and Sprung 2001):

- Fever
- Hypothermia
- Unexplained tachycardia
- Unexplained tachypnea
- Unexplained shock
- Peripheral vasodilation
- Differences/changes in mental status

Laboratory parameters (and invasive hemodynamic parameters) of sepsis include (Matot and Sprung 2001):

- Low systematic vascular resistance
- Increased cardiac output
- Increased oxygen consumption
- Leukocytosis
- Neutropenia
- Unexplained lactic acidosis
- Unexplained alteration in renal or liver function tests
- Thrombocytopenia/ disseminated intravascular coagulation
- Increased procalcitonin
- Increased cytokines

An ideal biomarker capable of identifying early onset of sepsis in burn patients needs to be reliable, easily measured, sensitive, and specific (von Heimburg et al. 1998). In the next section, the biomarker procalcitonin is evaluated as an identifier of burn patients susceptible to sepsis.

3.4   Procalcitonin as a Biomarker of Sepsis

Procalcitonin has emerged as a strong candidate for predicting the onset of infection, as well as the different severity levels of sepsis, regardless of the initiating injury (Uzzan et al. 2006; Viallon et al. 2008; Suárez-Santamaría et al. 2010; Mann et al. 2011; Brodská et al. 2013; Seoane et al. 2014; Ren et al. 2015). In healthy adults, serum PCT generally remains at an undetectable level, but PCT levels will quickly rise during a highly elevated immune response to infection (Reinhart et al. 2000; Lin and Yap 2017). With successful treatment, PCT levels return to homeostatic levels. For these reasons, PCT has been identified as one of the more well-established biomarkers of burn-induced sepsis. Additional biomarkers (e.g. IL-6, IL-8, neopterin, C-reactive protein, white cell count) have been identified and analyzed for their predictive capabilities of burn-induced sepsis (Harbarth 2001; Lavrentieva et al. 2007; Tasdelen Fisgin et al. 2010; Kaplan 2017), but no single measurement has been established as the consensus biomarker of choice. While there has been some controversy about the viability of procalcitonin as a biomarker of sepsis (Suprin et al. 2000; Tasdelen Fisgin et al. 2010; Seoane et al. 2014), it has been gaining acceptance with recent work, and a body of data exists which make it possible to successfully model the probability of sepsis as a function of % TBSA.

PCT is a 116-amino acid peptide normally synthesized in small amounts by thyroid C cells as a precursor to the hormone calcitonin. It is also produced by the neuroendocrine cells of the lung and intestine, and is released as an acute-phase reactant in response to inflammatory stimuli (Lin and Yap 2017). When a bacterial infection is present, bacterial products such as lipopolysaccharide (LPS) and lipotechoic acid (LTA) interact with toll-like receptors expressed on immune cells and induce a pro-inflammatory cytokine response. This initiates hypersecretion of PCT in extrathyrodial neuroendocrine tissues (parenchymal cells) (Kibe et al. 2011). In a positive feedback loop manner, leukocyte-derived cytokines can continue to augment blood cell

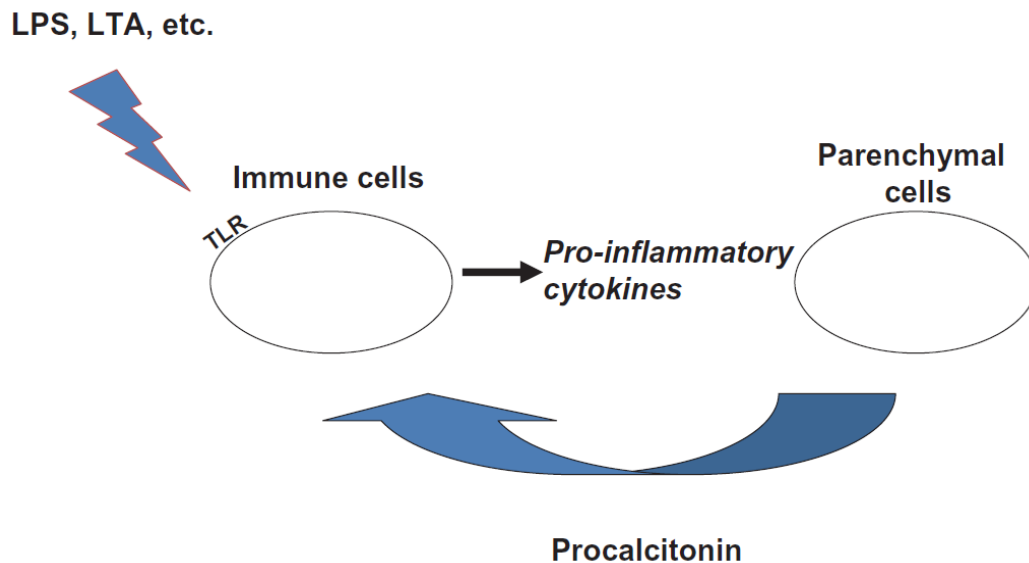production of these cytokines (Becker et al. 2010). Figure 3 provides an illustration of this process.

Figure 3. Illustration of the infection-induced procalcitonin feedback loop (Becker et al. 2010).

PCT levels quickly rise when a bacterial infection is present (four hours after onset of systematic infection, while hitting peak levels within eight to 24 hours) (Carsin et al. 1997; Reinhart et al. 2000; Lavrentieva et al. 2007; Kibe et al. 2011; Kim et al. 2012). A rare case of accidental hemodialysate contamination documented an individual infected with *Acinetobacter baumanii* who then became septic. PCT levels measured hours (Figure 4A) and days (Figure 4B) after the infection demonstrated a rapid increase, followed by a steady decrease (corresponding to a half-life of PCT, approximately 22.5 hours) over the time course of the septic episode (Brunkhorst et al. 1998; Reinhart et al. 2000).
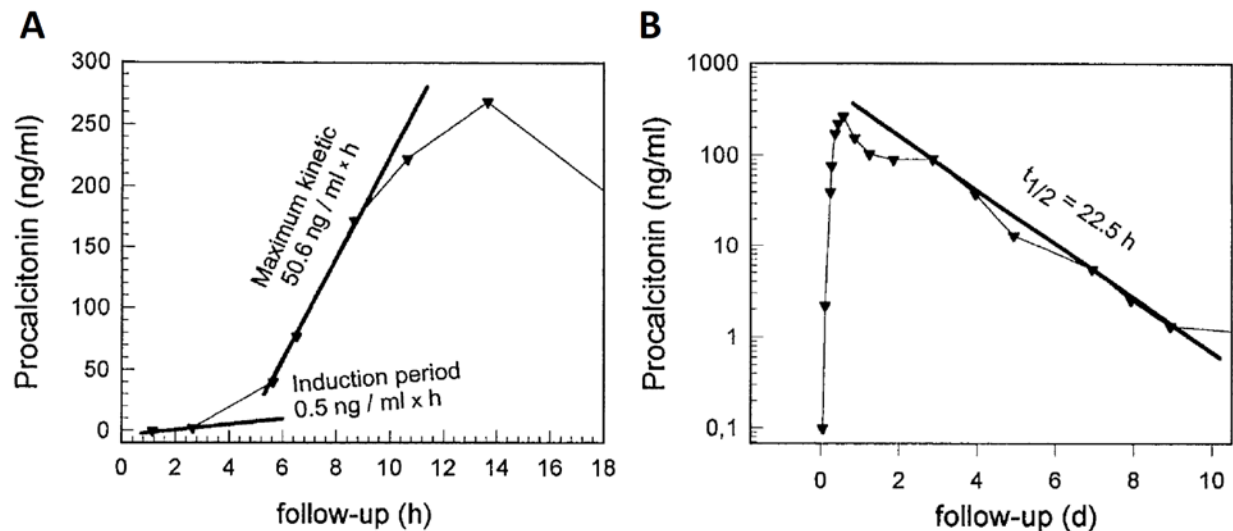
Figure 4. Kinetics of procalcitonin following bacterial infection, leading to sepsis(Brunkhorst et al. 1998; Reinhart et al. 2000).

While a correlation between TBSA and PCT admission levels cannot be clearly defined, a positive correlation between TBSA and median peak PCT levels during post-burn recovery has been reported (von Heimburg et al. 1998; Kim et al. 2012). PCT can be detected within three to four hours after burn, peak levels generally occur about 14 hours after stimulus, and serum PCT levels remain elevated for another 10 hours (Carsin et al. 1997; Reinhart et al. 2000; Lavrentieva et al. 2007; Kim et al. 2012). Recently, Wacker et al. (2013) performed a meta-analysis, using research standard criteria to narrow down 30 reports that evaluated PCT as a biomarker of sepsis. Each of these studies assessed cutoff PCT values obtained through receiver operating characteristic (ROC) analyses (Metz 1978; Zweig and Campbell 1993), finding that the values range from 0.1 to 15.75 ng/mL (Wacker et al. 2013).

As demonstrated by Wacker et al. (2013), there is a great deal of variability between PCT cutoffs established from ROC analyses to predict sepsis. We are confident that some of this variability can be attributed to patient demographics and injury type (Figure 5). For instance, in critically ill children, PCT cutoffs as high as 9.7 ng/mL and as low as 0.015 ng/mL have been identified as predictive of sepsis (Clec'h et al. 2006; Brodská et al. 2013). Alternatively, in adult burn patients the cutoff PCT values range between 0.534 ng/mL and 2.415 ng/mL (Balci et al. 2002; Bargues et al. 2007). Variability across patient and injury type (see Figure 5) makes it difficult to find consistent correlation between PCT levels and sepsis. By narrowing the scope of this biomarker to burn patients (Table 3) some of this variability can be reduced. Similar cutoff values were established in a more recent meta-analysis of PCT for diagnosing sepsis in burn patients (Cabral et al. 2016).
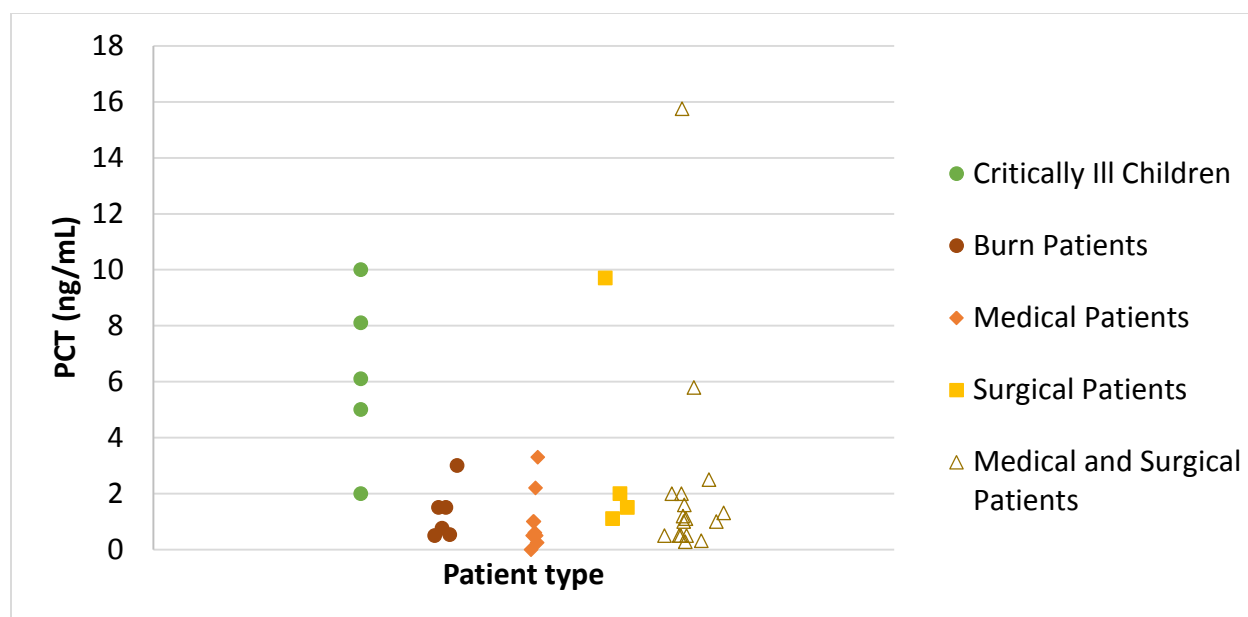
Figure 5. PCT sepsis thresholds from ROC analyses for different patient types.

Table 3. Sepsis-predicting PCT thresholds for burn patients established with ROC analysis.

PCT cutoff (ng/mL)	Sensitivity (%)	Specificity (%)	AUC*	Reference
0.5	100	89.3	0.97	Barati et al. (2008)
0.534	42.4	88.8	n.p.**	Bargues et al. (2007)
0.759	75.7	78.6	84.7	Cakir Madenci et al. (2014)
1.5	82	91.2	0.975	Lavrentieva et al. (2007)
1.5	88.3	92.3	0.966	Lavrentieva et al. (2012)
3	11	100	n.p.**	von Heimburg et al. (1998)

*AUC – Area under the curve
**n.p. – Not provided; ROC analysis by Ren et al. (2015)

In addition to predicting sepsis, PCT has been evaluated as a predictor of severity of sepsis for burn patients (Castelli et al. 2004; Viallon et al. 2008; Su et al. 2013). Furthermore, when adding PCT to standard clinical variables of moderate diagnostic value, the diagnostic certainty has been shown to increase, allowing health care workers to better tailor a treatment plan (Harbarth 2001).

In future work, we will reassess the predictive power of PCT as a biomarker of severity of sepsis as well as the potential for using multiple biomarkers, possibly with a multivariate approach.

Section 4. Methods

Our goal is to develop a model that predicts the probability that an individual will suffer from health complications attributable to infection after being exposed to a nuclear weapon environment. A nuclear detonation exposes individuals to radiation, thermal burns, and blast-related trauma, each which can contribute to the growth and spread of bacteria, fungi, and other harmful pathogens. The development infection is an inherently complex phenomenon and can proceed via multiple pathways; therefore, for this initial modeling effort, we have decided to focus solely on infection resulting from burn wounds, using a data-driven empirical approach instead of a mechanistic model. However, in this section, we briefly review the basics of mechanistic models of infection before discussing our approach.

Burn wounds kill and expose various layers of skin, creating an ideal environment for harmful microorganisms to spread and invade a human host (see Section 3 for more details). In the development a mechanistic model, it is important to take into account the variability of the events leading up to colonization of a burn wound. For instance, colonization will depend on the following in a stochastic manner: the size of the burn wound (measurements are imprecise; see Section 3.1), exposure to pathogens (varies by location of the casualty; see Section 3.2), and the strength of the individual's immune system. Due to the complexity of this phenomenon, many assumptions are required and there have been few attempts to develop completely mechanistic models. The models that do exist generally focus on bacterial infection spread by quorum sensing. Quorum sensing is a very common and well understood mechanism which describes development of bacterial infection found in burn wounds.

Ideally, a mechanistic quorum sensing model would predict the time-dependent spread of bacteria in a burn wound and provide a quantifiable rate of the spread of infection. This could be used to make predictions about the timing and severity of septicemic episodes. Previously developed computational models of quorum sensing include partial differential equation (PDE) models (Dockery and Keener 2001; Chopp et al. 2002; Koerber et al. 2002; Chopp et al. 2003; King et al. 2003; Anguige et al. 2006; Duddu et al. 2009) and agent-based models built on cellular automata principles (Picioreanu et al. 1998; Hermanowicz 2001; Kreft et al. 2001; Picioreanu et al. 2004; Xavier et al. 2005). These models can be computationally expensive, and often consist of many parameters that are difficult to verify experimentally.

There are many uncertainties and details about burn-wound infection that are difficult to capture with a mechanistic model. We decided to develop a probabilistic model of sepsis, a life-threatening endpoint of severe infection, using the biomarker of sepsis, PCT. Alternatively, we could directly model the relationship between burn size and bloodstream infection (see Shupp et al. (2010)), but we have decided to model PCT for reasons discussed in Section 1. Clinical data is available to estimate PCT levels from a % TBSA burn size, and PCT has been evaluated in many studies to predict the probability of sepsis (see Section 3.4 for more details). Our approach is not limited to a single pathogen, as many of the mechanistic models are, and avoids the need to develop parameters for individual types of invasive microorganisms. We apply a dose response approach, which makes it easy to build stochasticity into our model that is supported by clinical data. Furthermore, a model built around an easily-accessible biomarker may be useful for clinical analysis. The following sections describe the development of this model.

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4.1   Mapping Burn Size to PCT Levels

Many studies relate % TBSA to PCT levels (Carsin et al. 1997; von Heimburg et al. 1998; Abdel-Hafez et al. 2007; Lavrentieva et al. 2007; Kim et al. 2012). Unfortunately, these studies generally only report burn sizes and PCT levels for two or three groups of patients. For instance, Abdel-Hafez et al. (2007) reported average PCT levels of children with % TBSA burns above and below 30%, and von Heimburg et al. (1998) reported average PCT levels and average % TBSA burns for three groups of burn patients: non-septic survivors, septic survivors, and septic non-survivors. Fortunately, Kim et al. (2012) provided sample statistics of PCT measurements for 175 burn patients (142:33 male:female ratio; median age 45; range 3-86). PCT values (minimum, maximum, and median), measured within the first 48 hours of admission were reported for 10 groups of burn ranges (Table 4). There is a clear trend between increasing burn size and median PCT levels (Figure 6). While the median PCT values appear to increase exponentially with burn size, the PCT ranges are extremely large for each burn group. This variability is expected due to the inexactness of burn measurements, variability in environmental exposures, inter-individual differences in immunity, and other factors (see Section 3 for a more detailed discussion).

Table 4: PCT levels after burn (Kim et al. 2012).

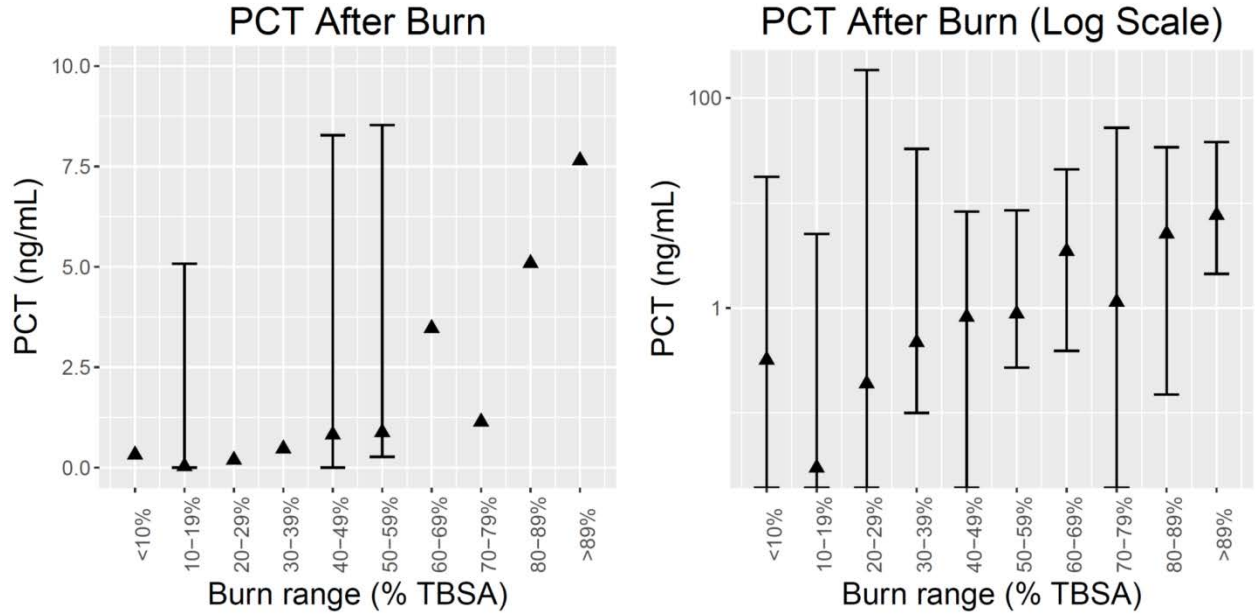| Burn Range (% TBSA)	Median PCT (ng/mL)	Min PCT (ng/mL)	Max PCT (ng/mL)	n
1-10	0.32	<0.05	17.78	14
10-20	0.03	<0.05	5.08	20
20-30	0.19	<0.05	184.44	32
30-40	0.47	0.1	32.77	21
40-50	0.82	<0.05	8.28	20
50-60	0.88	0.27	8.53	8
60-70	3.47	0.39	20.94	19
70-80	1.14	<0.05	52.03	15
80-90	5.09	0.15	33.9	14
90-100	7.65	2.11	38.03	12

Figure 6. Sample statistics for PCT levels of burn patients (Kim et al. 2012). Bars represent min and max values, and triangles represent median values.

Due to the stochastic nature of infection, we have decided to estimate PCT levels with probability distributions that reflect the data reported in Kim et al. (2012). While this limits us to using data from one study, we found that the relationship between burn size and PCT levels is comparable to measurements reported in other studies (Carsin et al. 1997; von Heimburg et al. 1998; Abdel-Hafez et al. 2007; Lavrentieva et al. 2007; Kim et al. 2012). This approach will help capture the random nature of infection, supported by clinical use of a biomarker which indicates the severity of sepsis expected from a burn-induced injury. The following assumptions were made when constructing the model:

- Burn ranges cover up to the lower bound of the subsequent burn range (e.g. 20-29% actually means 20-30%).
- Because the PCT values for each burn range are right-skewed and non-negative, we assume that each distribution is log-normal. Log-normal distributions are uniquely identified by scale (σ) and location (μ) parameters.
- Due to the direct relationship between μ and the median of a log-normal distribution, we chose μ for each distribution such that the median (m) of the distribution matched the median of the data samples ($m = e^{\mu}$).
- For each burn range, we only have three sample statistics: the number of individuals (n), the minimum PCT level (a) and the maximum PCT level (b). Because many of the minimum values are reported as, "<0.05 ng/mL", we have set a=0.05 for these cases. For the 1-20% TBSA group, we let n=34 (the total of the 1-10% and 10-20% TBSA groups), and we set a=0.05 and b=17.78, the maximum PCT value of the 1-10% TBSA group.

In addition to the above assumptions, we have combined the data from the 1-10% and 10-20% TBSA bins. The 10-20% TBSA group has a small range (0, 5.08) and an extremely small median

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(0.03), which would alone lead to a distribution with most of its density near 0. We approximated the median of the 1-20% TBSA group as the mean of the 1-10% and 10-20% TBSA median values. Furthermore, we used two approaches to estimate σ for each distribution. These two approaches are explained in the following subsections.

4.1.1. Approach 1 (Closed form Estimation)

In Wan et al. (2014), normal distribution parameter estimates (mean and standard deviation) were derived using various combinations of limited sample statistics. In a particular instance, equivalent to our situation, only the min (a), max (b), median (m) and number of samples (n) were provided. From these values, Wan et al. derived estimations of the mean and standard deviation of the corresponding normal distribution. Using the same approach, and the fact that a log-transformed log-normal random variable is normally distributed, we can acquire an estimate of the scale parameter (σ), which we provide in Equation (1):

$$\sigma \approx \frac{\log(b) - \log(a)}{\xi(n)} \tag{1}$$

where $\xi(n)$ is provided for each value of $n \leq 50$ in Table 1 of Wan et al. (2014).

4.1.2. Approach 2 (Monte Carlo Estimation)

The second approach we used for estimating the scale parameter of a log-normal distribution given the reported simple statistics (min (a), max (b), median (m), and number of samples (n)) is a random sampling, or Monte Carlo (James 1980) approach. We estimated the scale parameter, σ, by optimizing a cost function, $C(\sigma)$, that penalizes the choice of σ based on the ability of the distribution to reproduce the sample statistics through random sampling. That is, given a value for σ_s, $C(\sigma_s)$ is computed as follows:

1. The lognormal distribution, $\ln N(\mu, \sigma_s)$, is randomly sampled n times to generate $X_{i,1}$ ($i = 1, \ldots n$).
2. Step 1 is repeated N times to generate $X_{i,j}$ ($i = 1, \ldots, n, j = 1, \ldots, N$). N was chosen to be large (10,000), but this value had little effect on the results.
3. The minimum, $X_{a,j}$ and maximum, $X_{b,j}$, of each sample set are specified for each $j = 1, \ldots, N$.
4. Mean values of the minimum and maximum of the random samples are used to estimate a and b: $\tilde{a} = \frac{1}{N}\sum_{j=1}^{N} X_{a,j}$ and $\tilde{b} = \frac{1}{N}\sum_{j=1}^{N} X_{b,j}$.
5. $C(\sigma_s) = (a - \tilde{a})^2 + (b - \tilde{b})^2$.

This second approach simulates the experimental scenario repeatedly, choosing the distribution parameter which appears most often, and is thus most likely to appear in a random sample. We have chosen to use Approach 1 to estimate the parameters, and Approach 2 to validate the parameter choices derived using Approach 1.

4.2   Mapping PCT Levels to Sepsis

After establishing a link between burn severity (% TBSA) and PCT levels, the next challenge is to predict if a burned individual will become septic from their PCT measurement. Many studies have evaluated the use of PCT as a predictive biomarker of sepsis, establishing threshold values using ROC analysis (reviewed in Section 3.4). Here, we focus specifically on burn patients (Table 3). We select one of these values as a cutoff to predict whether or not an individual will become septic.

The threshold values in Table 3 range from 0.5 to 3 ng/mL. While this is not an extremely large range, it is important to select the most suitable value for our model. The lowest value (0.5 ng/mL, established in Barati et al. (2008)) would be the most conservative choice in terms of capturing the highest percentage septic cases (highest true positive rate). However, choosing a threshold that is too low will cause the model to over-diagnose septic patients (high false positive rate), resulting in an overestimate of the required resources needed to treat these individuals.

We have chosen the mid-ranged threshold value of 1.5 ng/mL, established in Lavrentieva et al. (2012). In Lavrentieva et al. (2012), the PCT measurement was taken within 24 hours of admission. This timeframe agrees with the findings of Kim et al., who reported that, "procalcitonin concentrations within the first 48 hours, especially between 14 and 24 hours, after burn injury serve as a useful prognostic indicator for sepsis and mortality in burn patients" (Kim et al. 2012). Lavrentieva et al. (2012) is also the only study to use the newest diagnostic criteria for sepsis, established by the consensus panel in Greenhalgh et al. (2007) that defined specific criteria for identifying septic burn patients (see Table 2).

Section 5. Results

For each binned burn range, the ICE model has been established with an associated log-normal distribution of PCT values. The scale (σ) and location (μ) parameters of these distributions are presented in Table 5. The scale parameters acquired using approach 1 (Section 4.1.1) and approach 2 (Section 4.1.2) are presented for comparison. In general, the scale parameters chosen from these two methods are similar. Although some of the values differ, the distributions constructed with these values are similar (Figure A1 - Figure A9).

Table 5. ICE model parameters.

Burn Range (% TBSA)	μ	σ (approach 1)	σ (approach 2)
1-20	-1.74	1.40	1.94
20-30	-1.66	1.99	2.71
30-40	-0.76	1.98	1.92
40-50	-0.20	1.37	1.13
50-60	-0.13	1.21	1.33
60-70	1.24	1.08	0.90
70-80	0.13	2.00	1.84
80-90	1.67	1.59	1.01
90-100	2.03	0.89	0.89

Three normalized distributions of the ICE model (1-20, 50-60, and 90-100% TBSA) are provided in Figure 7. For comparison, the median PCT levels of the Kim et al. (2012) data have been plotted against the midpoint of the %TBSA interval (circles), and this data has been fit with an exponential function (solid line) to illustrate the trend in this data. These three distributions demonstrate the increasing spread of the PCT distributions corresponding to increasing burn severities. Values predicted by the ICE model are presented in Table 6 including the mean PCT value (expected PCT level) and the bounds of a 90% probability mass. The bounds establish where five percent of the probability mass lies below and above, respectively. The last column of Table 6 provides the probability of sepsis, defined as the probability that a random sample from the associated log-normal distribution will lie above our chosen threshold value of 1.5 ng/mL (see Section 4.2).
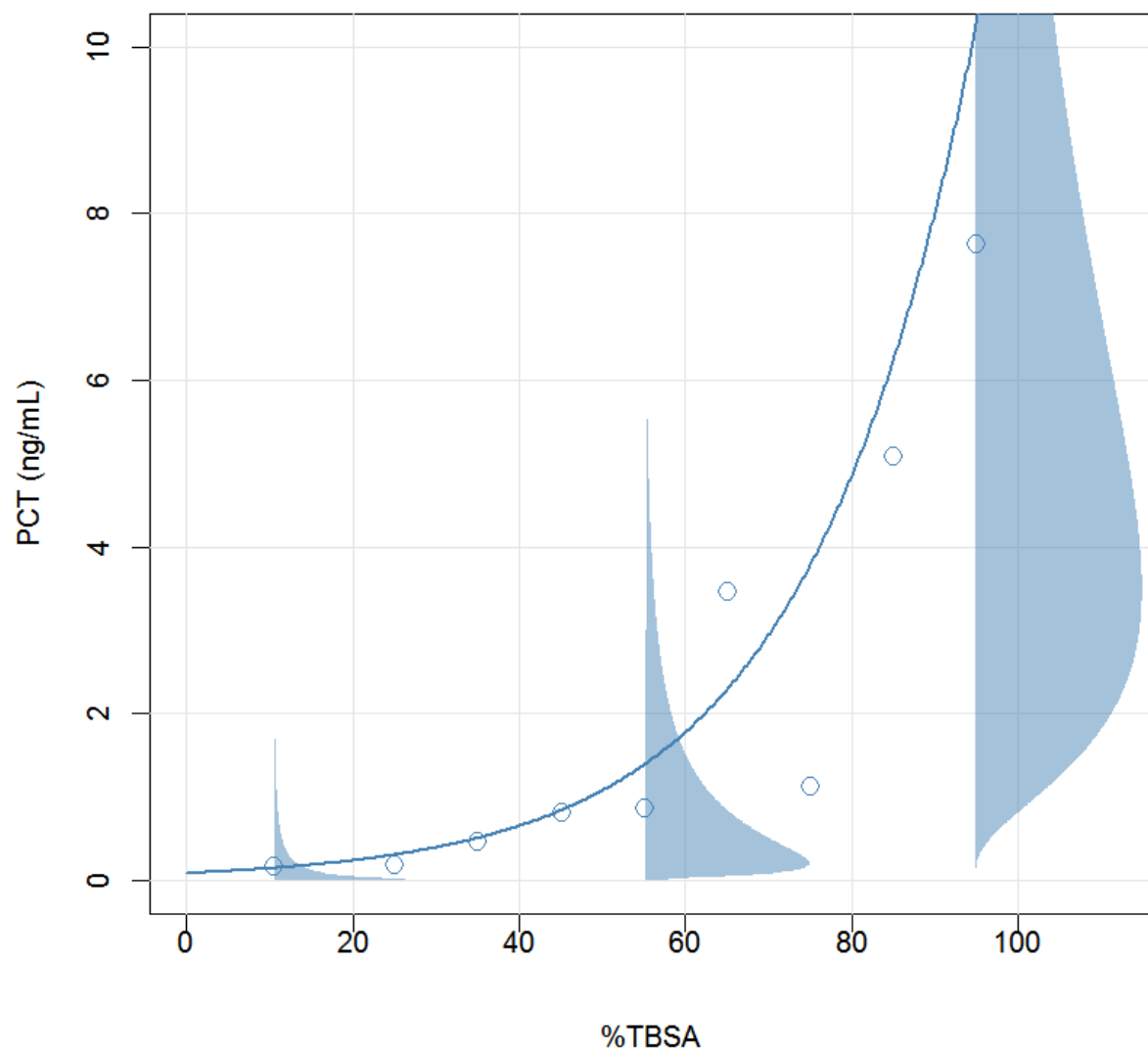
Figure 7. Three distributions of the ICE model compared to median PCT values.

Table 6. Predicted values from the ICE model.

Burn Range (% TBSA)	Expected PCT level (ng/mL)	Bounds containing 90% of the probability mass	Probability of sepsis*
1-20	0.47	(0.02, 1.76)	0.06
20-30	1.36	(0.01, 4.97)	0.15
30-40	1.52	(0.04, 5.85)	0.22
40-50	2.09	(0.09, 7.78)	0.33
50-60	1.84	(0.12, 6.47)	0.33
60-70	6.22	(0.59, 20.50)	0.78
70-80	8.44	(0.04, 30.65)	0.45
80-90	18.04	(0.37, 69.70)	0.78
90-100	11.34	(1.78, 32.92)	0.97

*This value is calculated using the probability of exceeding 1.5 ng/mL.

Some of the probability values reported by the ICE model do not follow the general monotonic trend. In particular, there is a jump in the probability of sepsis (0.33 to 0.78) in the 60-70% TBSA range that is followed by a drop (0.78 to 0.45) in the 70-80% TBSA range. While it is difficult to distinguish which of these values are significant, we believe artifacts such as this are unavoidable. As we discussed in Section 3, variability in this type of data is expected due to the inconsistencies in the measurement of TBSA, as well as the factors that lead up to infection and sepsis. Furthermore, discrepancy in the model for higher % TBSA values should not have a large impact on casualty estimation, as we expect burns in an IND scenario to mostly be caused by flash burns, which are not expected to exceed 50% TBSA (see Section 1). In the future, we plan to revisit this variability and determine if improvements can be made to the model.

Section 6. Discussion

The ICE model has been developed to extend the capabilities of DTRA's casualty estimation toolset. Although the model does not yet address combined injury (see Section 1), the model estimates the susceptibility of burned nuclear weapon casualties to sepsis, a lethal, but potentially treatable health complication. In an IND event, the distribution of burned individuals would depend on nuclear weapon parameters such as yield and height of burst (Glasstone and Dolan 1977). Given a distribution of burned individuals not immediately killed by the blast, the ICE model can be used to predict the number of casualties vulnerable to sepsis. This information can then be used to improve casualty stream estimations for an IND scenario, particularly where many individuals are burned.

As with any mathematical model, the accuracy of ICE depends on the set of assumptions used in its development. For instance, we have taken a phenomenological approach and built the model as a set of probability distribution functions, as opposed to using a mechanistic approach that explicitly considers the underlying biology. Also, we have used PCT as an intermediary between burn size and sepsis, instead of establishing a direct relationship between burn size and infection. We chose to include PCT in the model because of the clinical value of PCT, the availability of data, and the added potential of establishing a mechanistic model (see Section 1).

The ICE model has also been developed under the assumption that clinical data can be used to represent IND casualties. The studies used to define the model (Kim et al. 2012; Lavrentieva et al. 2012) consisted of burn patients who were immediately able to receive full medical care. Furthermore, the patients in these studies did not have serious pre-existing conditions, and were not suffering from other types of injuries. In reality, access to medical care, co-morbidities, combined injuries, and many other factors would contribute to the susceptibility of nuclear weapon casualties to infection. Quantifying the added impact these factors have on vulnerability to sepsis is a future aim for the ICE model.

The model makes certain assumptions regarding use of PCT as a biomarker for burn-related infection, as well as the appropriateness of the data used in developing the probabilistic distribution functions. Within the domain defined by PCT data, we believe that the ICE model provides a reasonable starting point that will improve casualty estimation for burn-related infections. However, there are limitations to this phenomenological approach, and we recognize that the predictive ability of the model could be improved by developing a biological representation of the infection process. The following section describes future efforts that we believe will continue to improve and enhance the applicability of ICE to predict burn-related infections in a combined injury environment.

Section 7. Future Work

The ICE model is a first attempt to predict infection-induced complications of nuclear weapon casualties. Infection is an extremely complex phenomenon dependent on many stochastic contributing factors. As a result, in order to make the modelling tractable, we have focused specifically on sepsis (instead of infection generally), and have derived a phenomenological model based on standard statistical methodology. While we believe that this represents a significant step forward in the capabilities in the HENRE models, representing an important case in the practical application of the model and well supported by available data, there is much work left to be done. Future development will be directed toward increasing the capabilities of the model, reducing the number of required assumptions, expanding the data used in model development, and reducing overall uncertainty in the outputs. Some directions for future work include:

- Combined injury modeling – predicting the added influence of blast and radiation effects on the risk of sepsis would improve the capabilities of the model.

- Time-dependent spread of infection – a mechanistic model of quorum sensing, for instance, could help capture the rate at which infection spreads. This information could be useful for predicting the timing of sepsis.

- Severity of sepsis – the model currently only predicts the incidence of sepsis. The predictive value of PCT for the severity of sepsis (SIRS, sepsis, and septic shock) should be revisited.

- Additional biomarkers – biomarkers in addition to PCT have been evaluated as predictive biomarkers of sepsis in burn patients. These biomarkers should be re-evaluated and even considered in conjunction with PCT (multivariate approach) to improve sepsis predictions.

- Treatment levels and demographics – the current model, as it is built on clinical data, operates under the assumption that the burned individual receives medical care. In an IND scenario, the outcome of individuals will vary greatly depending on the level of medical care they can receive as well as their demographics (age, gender, etc.) (Gomez et al. 2009; Keen et al. 2010).

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Section 9. Abbreviations, Acronyms and Symbols

ACCP	American College of Chest Physicians
ARA	Applied Research Associates, Inc.
AUC	Area under the curve
DTRA	Defense Threat Reduction Agency
HSRDIPT	Human Survivability R&D Integrated Program Team
ICE	Infection Casualty Estimation
LPS	Lipopolysaccharide
LTA	Lipotechoic acid
n.p.	Not provided
PCT	Procalcitonin
PDE	Partial differential equation
PDF	Probability density function
ROC	Receiver operating characteristic
SCCM	Society of Critical Care Medicine
SIRS	Systematic inflammatory response syndrome
TBSA	Total body surface area
TLR	Toll-like receptor

Appendix A. ICE Model Distributions

In this report, probability density functions (PDFs) were derived to estimate the PCT levels for specific burn ranges (1-20% TBSA, 20-30% TBSA, etc.), compared to the data reported in Kim et al. (2012). Each distribution was assumed to be log-normally distributed, where the location parameter (μ) was chosen such that the median of the distribution matched the median of the sample reported in Kim et al. (2012) (see Section 4.1). The scale parameter (σ) from each distribution was derived using two different approaches. Approach 1 was used to set the scale parameters for the ICE model (Section 4.1.1), and Approach 2 was used as validation (Section 4.1.2). The PDFs for each burn range, comparing the two approaches, are provided in Figure A1 - Figure A9, where a vertical dashed line represents our chosen cutoff value, 1.5 ng/mL, predictive of sepsis.

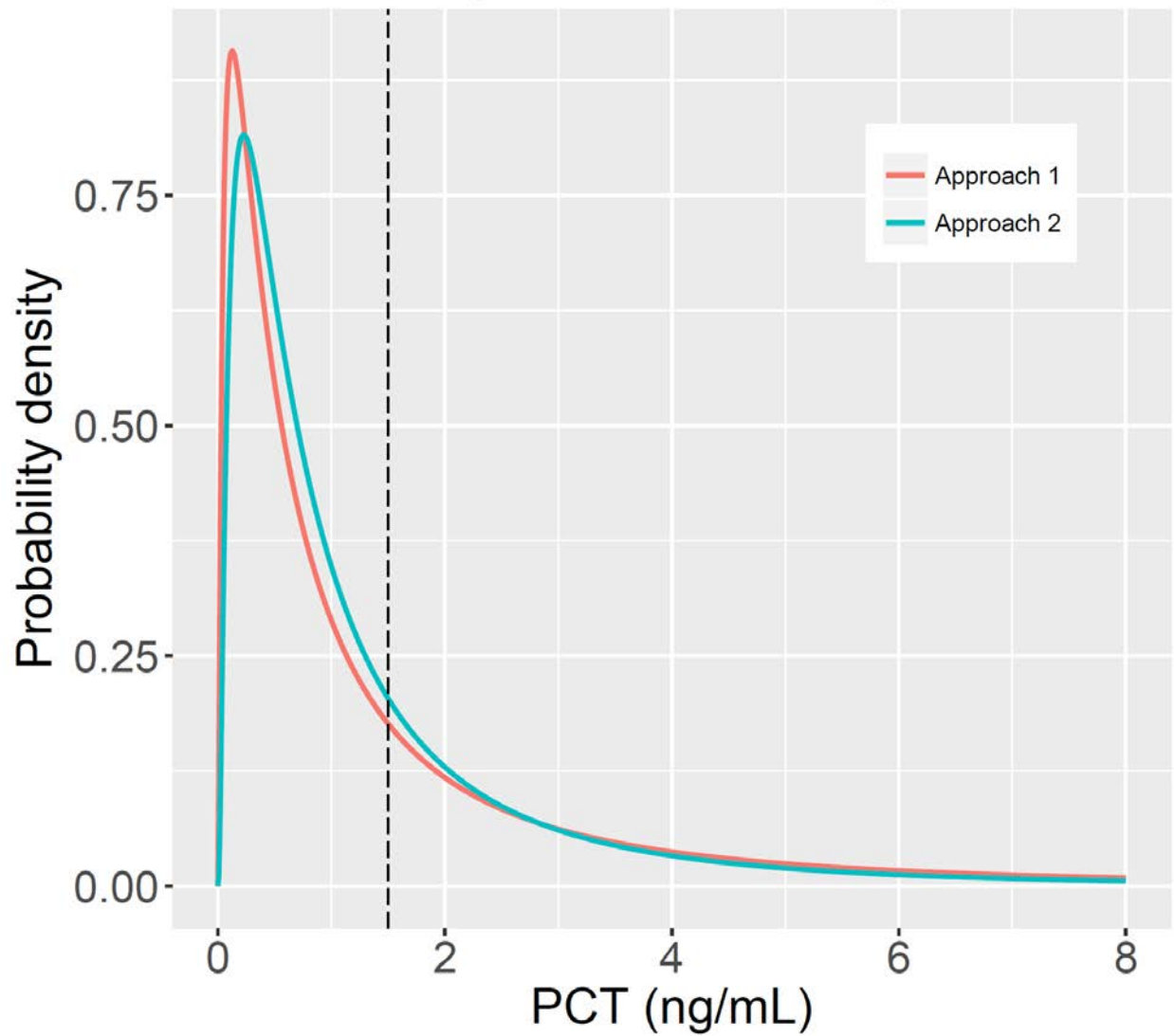# Probability Distributions
(1−20% TBSA)
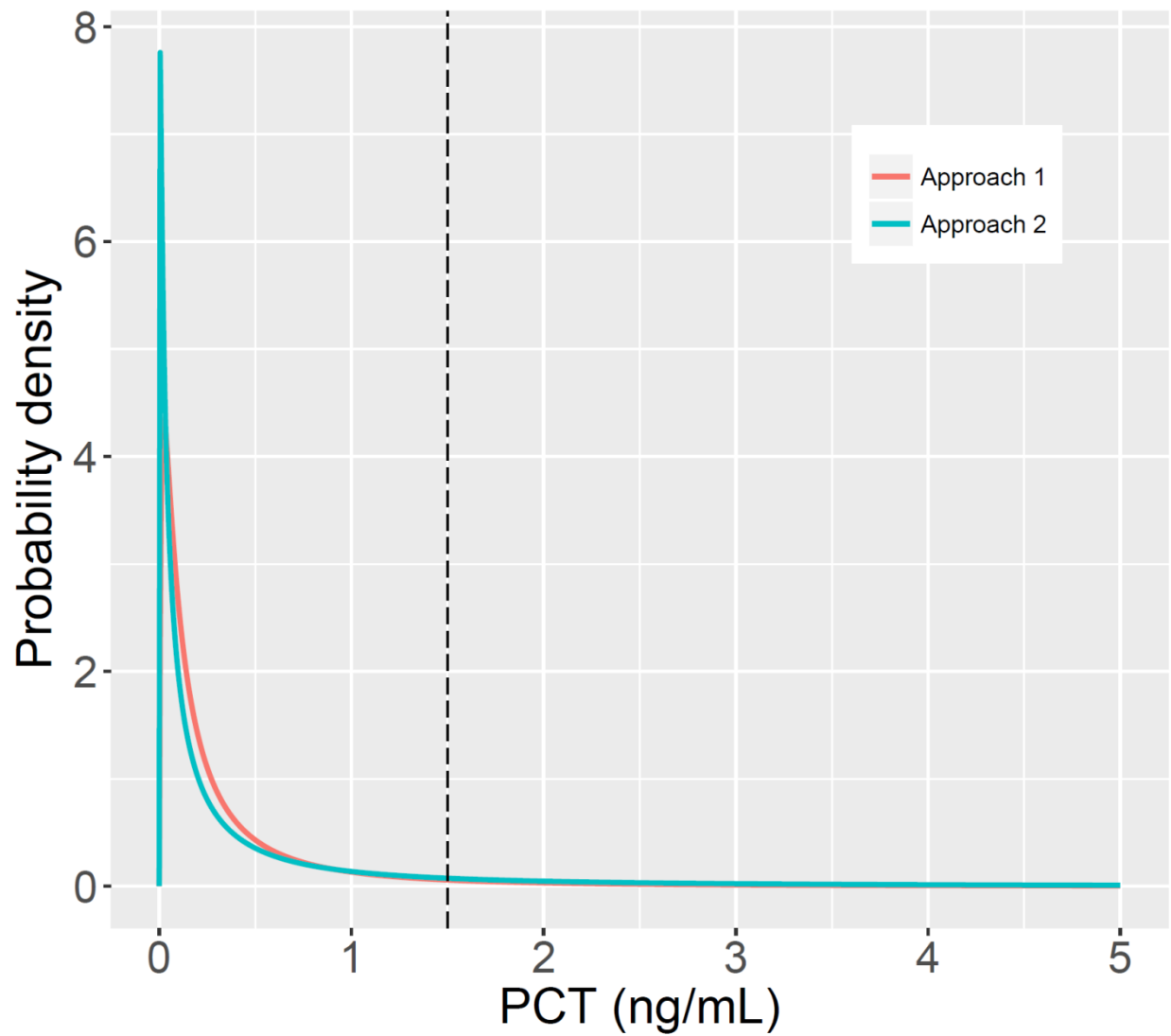
Figure A1. Probability density functions derived from two approaches (1-20% TBSA).
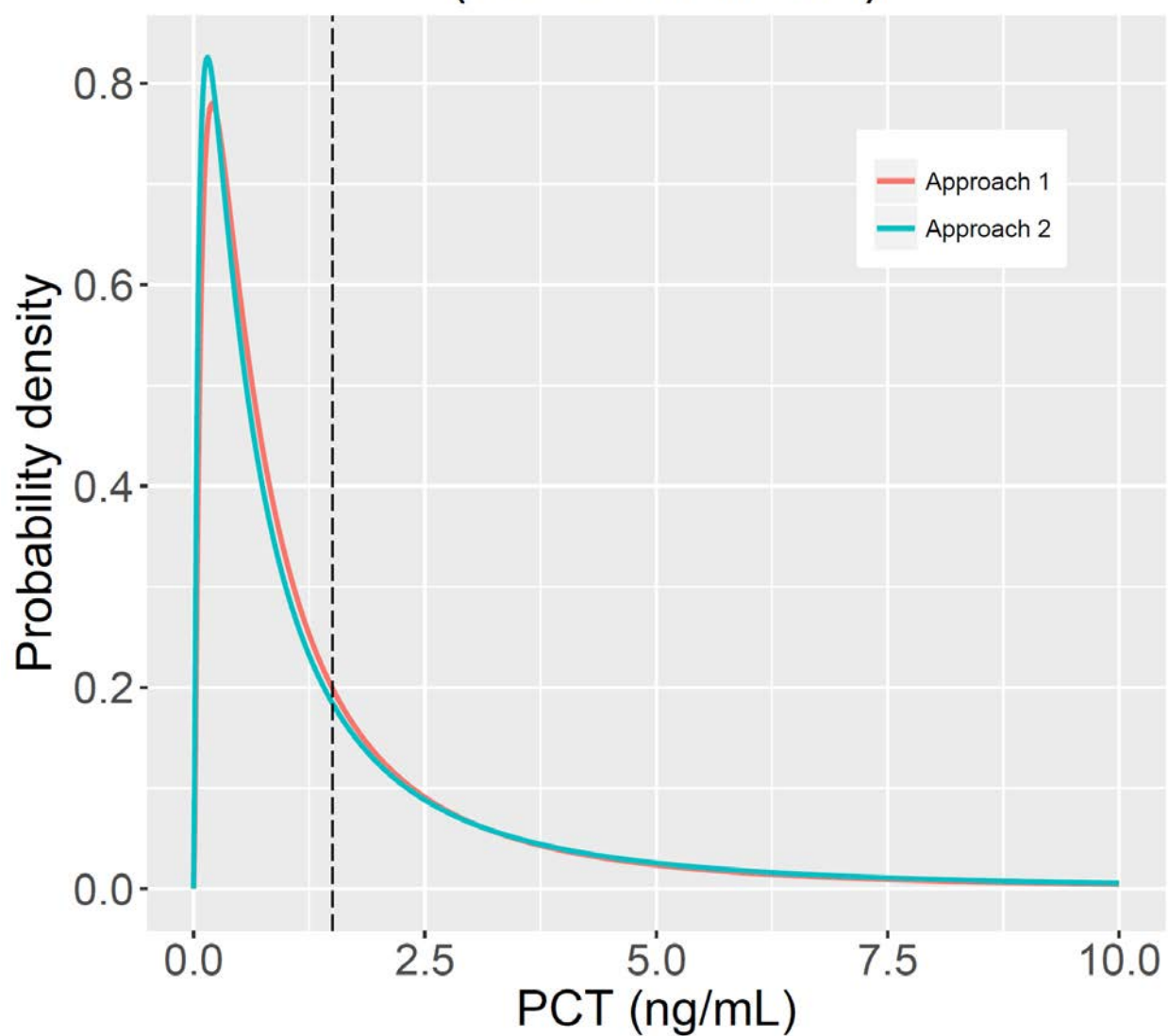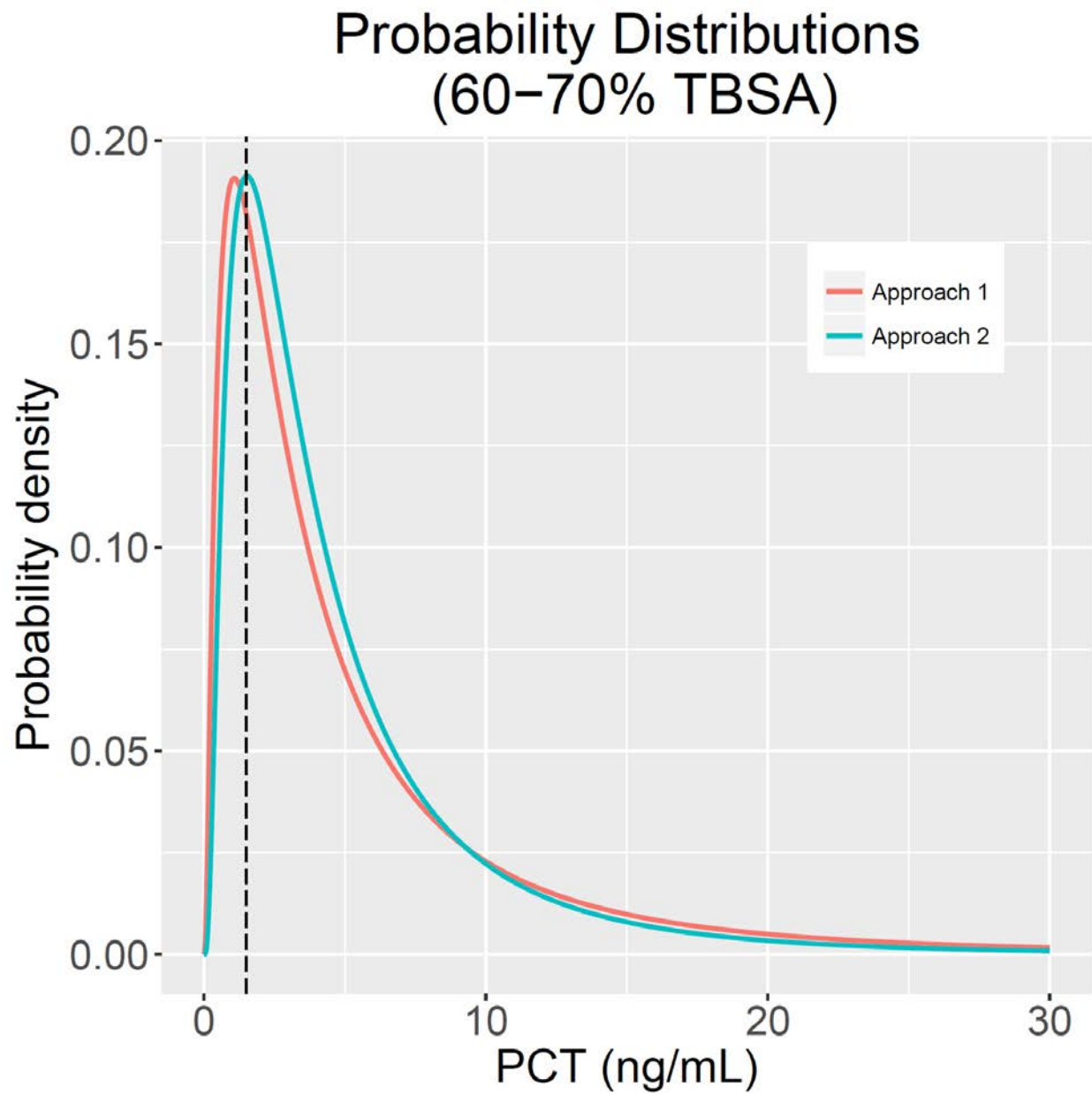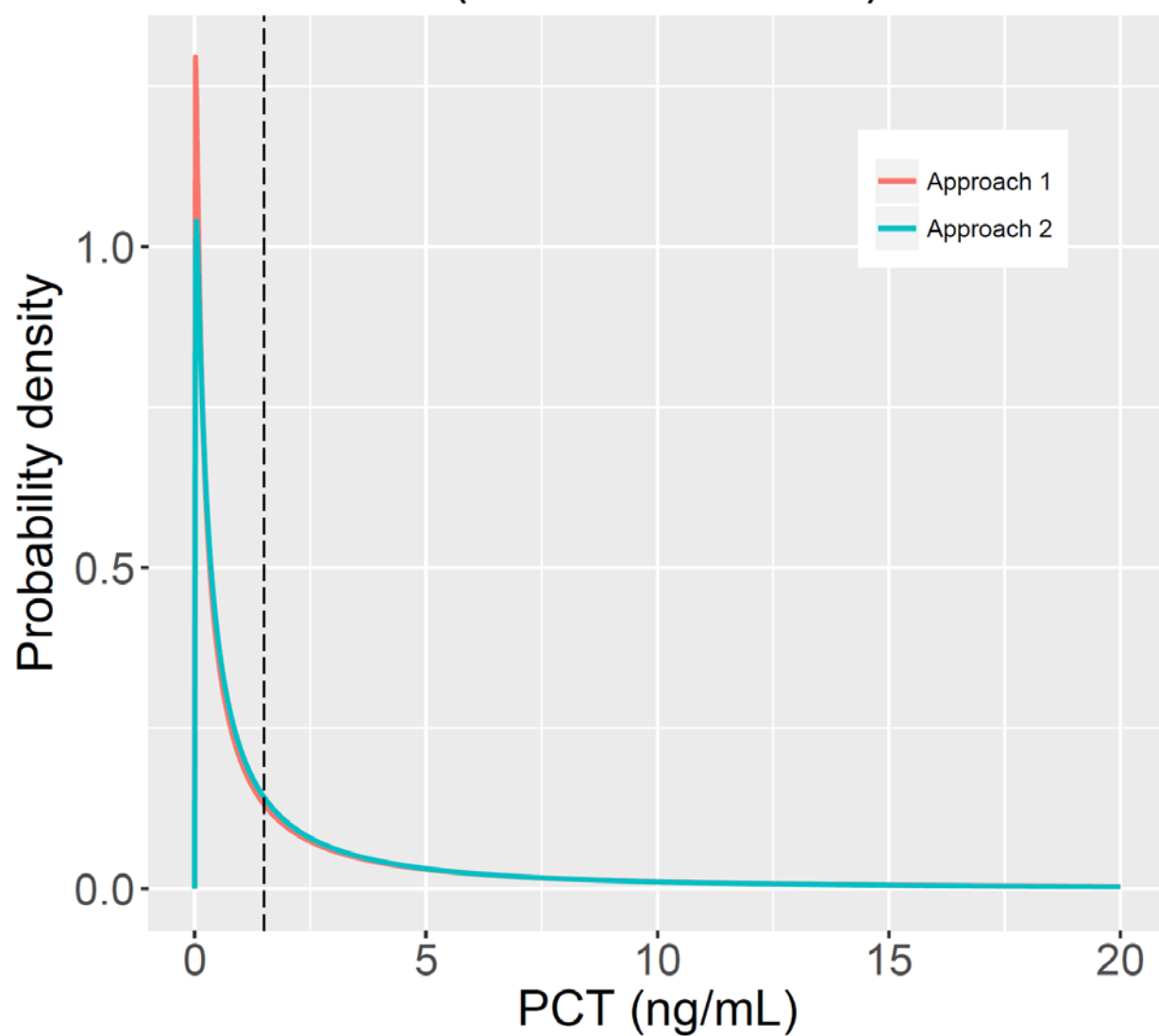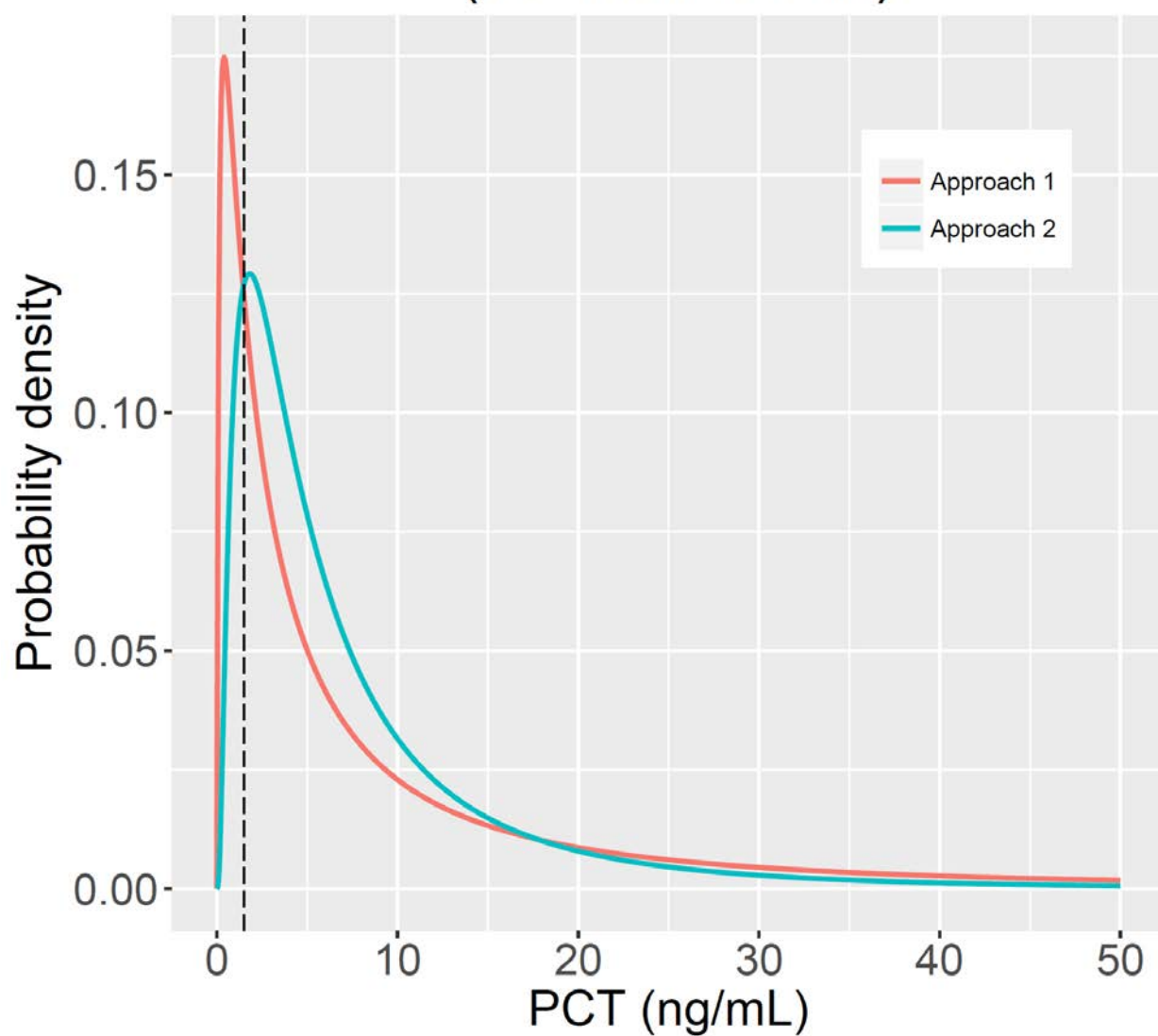
Probability Distributions
(20−30% TBSA)
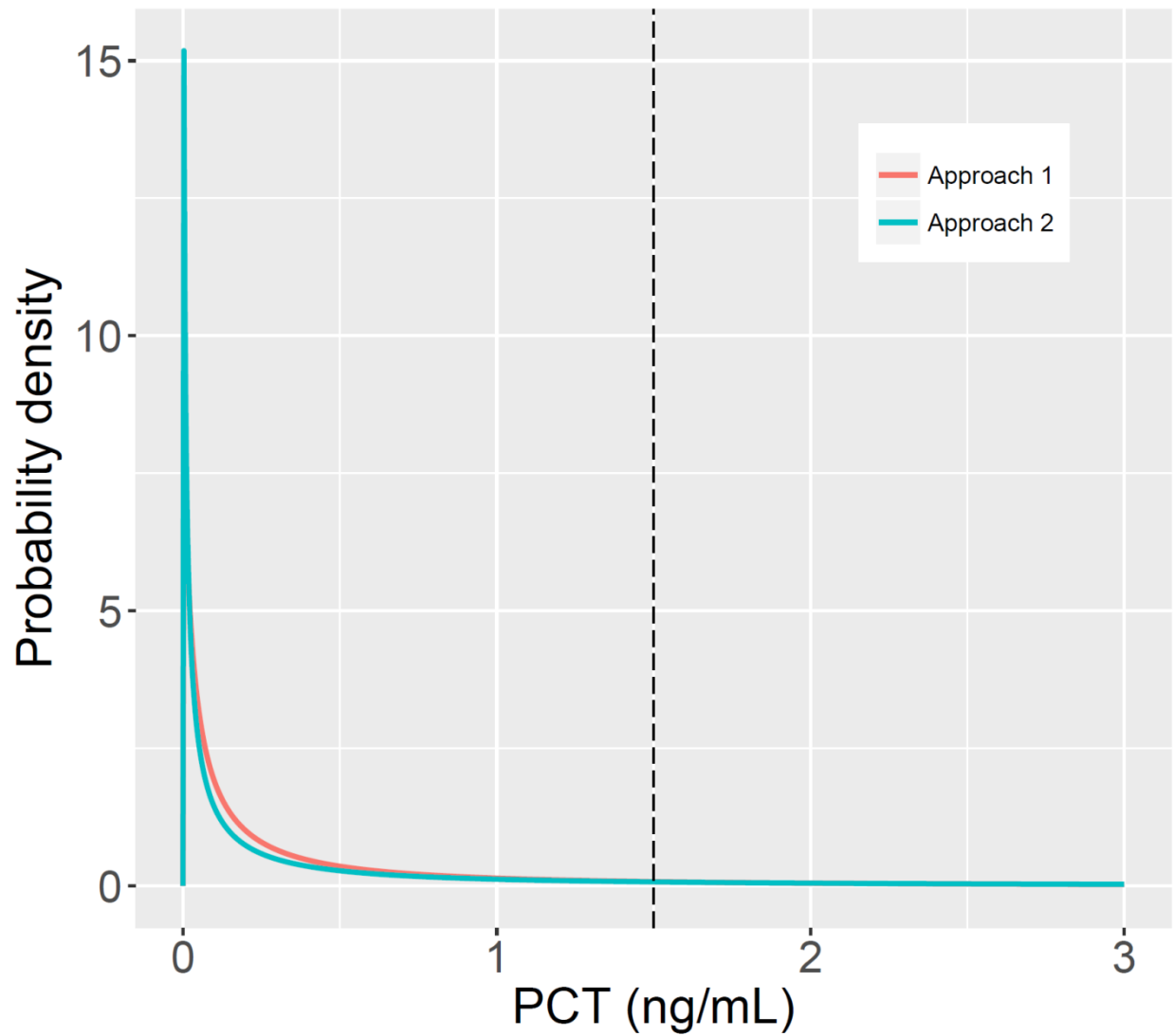
Figure A2. Probability density functions derived from two approaches (20-30% TBSA).
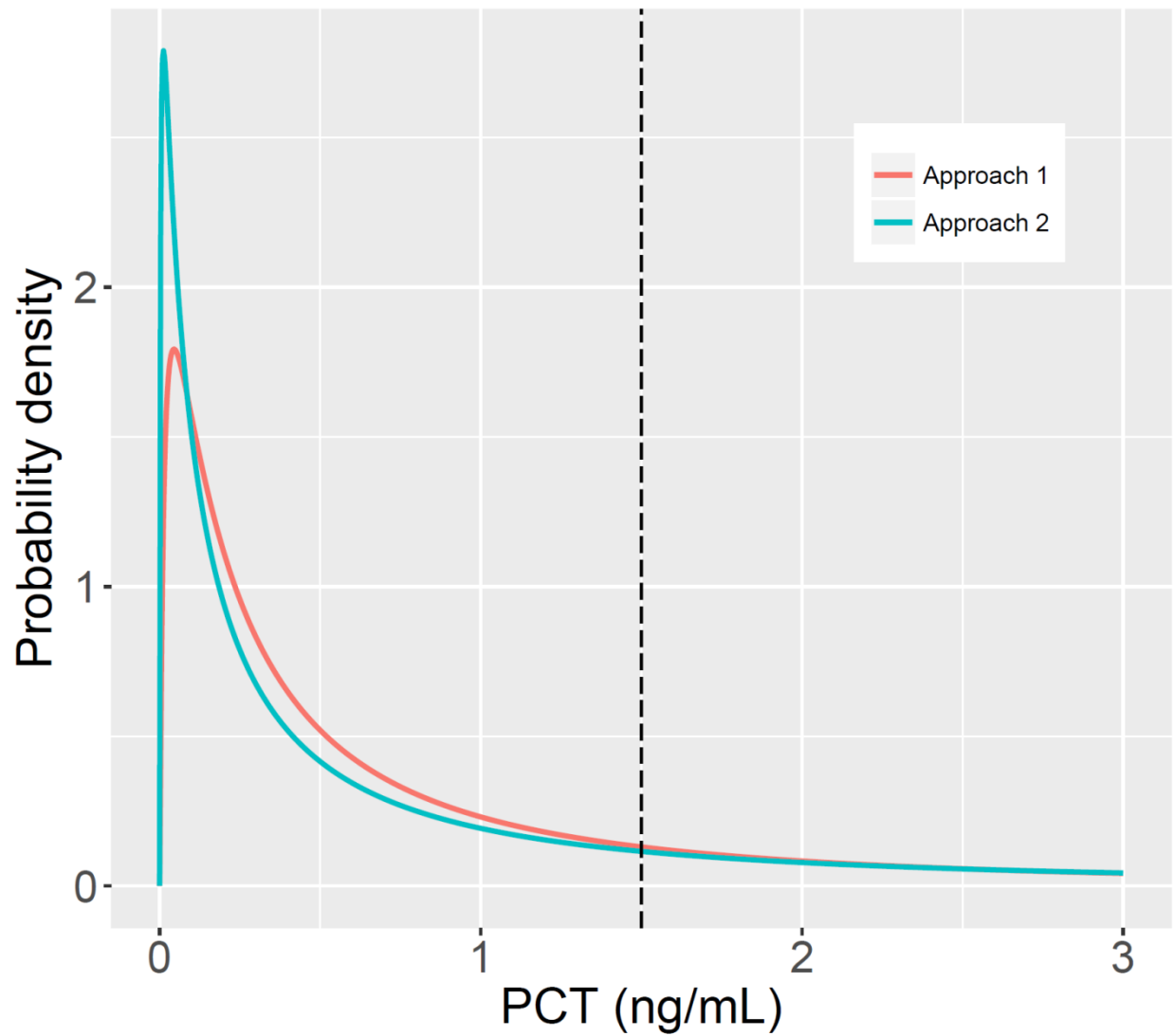
Figure A3. Probability density functions derived from two approaches (30-40% TBSA).

Figure A4. Probability density functions derived from two approaches (40-50% TBSA).

Figure A5. Probability density functions derived from two approaches (50-60% TBSA).

Figure A6. Probability density functions derived from two approaches (60-70% TBSA).

Figure A7. Probability density functions derived from two approaches (70-80% TBSA).

Figure A8. Probability density functions derived from two approaches (80-90% TBSA).
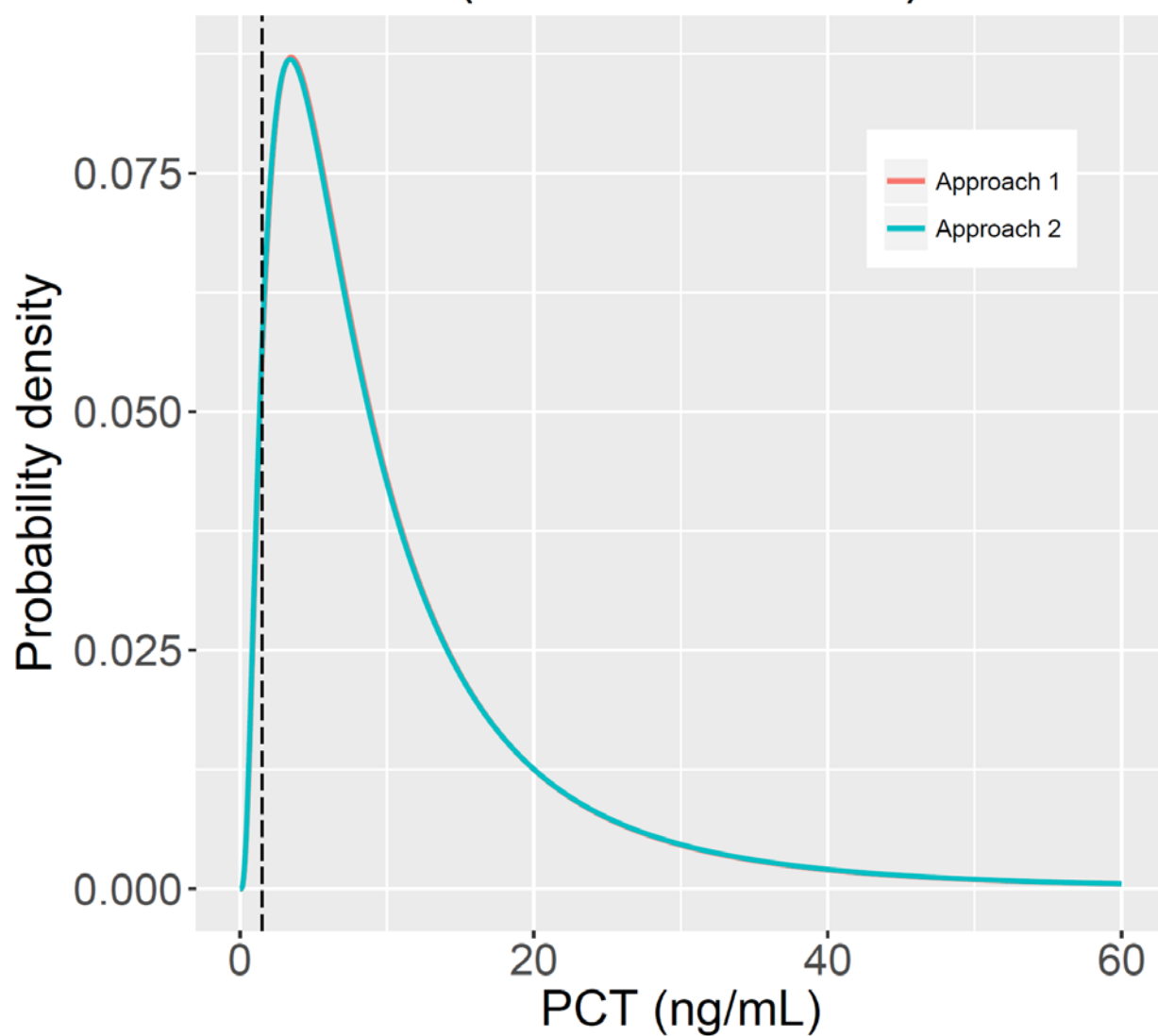
Figure A9. Probability density functions derived from two approaches (90-100% TBSA).